

Vascular Proliferation of the Thyroid: Potential Histopathological Pitfall as a Consequence of Fine Needle Aspiration

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Short Title: Post FNAB Thyroid Neovascularization

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Abstract

Objective: Fine needle aspiration biopsy (FNAB) can cause reactive histopathological changes including commonly haemorrhage and granulation tissue. Literature describing vascular proliferation after FNAB is sparse. We aimed to describe neovascularization in the thyroid gland specimens as a consequence of FNAB.

Study Design: We analysed all thyroid histopathological specimens from the Fimlab Laboratories within 2010-2013 for neovascularization and distortions in the accompanying tissue. We evaluated HE-stained slides and CD31, podoplanin and Ki-67 immunostained slides.

Results: We observed vascular proliferation in 64 specimens (out of 787 specimens, 8,1%). In these patients the mean age was 62 years; 43 were females and 21 males. A previous FNAB data were available in 49 cases (76.6%). In 51 cases (79.7%), the neovascularization occupied less than 5% area. The vessel dilatation was moderate in 28 cases (43.8%) and low in 20 cases (31.3%). In tumours, neovessels were detected within the tumour and in surrounding tissue.

Conclusions: Post-FNAB tissue samples include dilated newly formed vessels, which pathologists should differentiate from rare thyroid vascular tumours. The proposed mechanism is traumatically induced haemorrhage followed by hematoma and thrombosis that resolves by re-canalization. The knowledge of tissue alteration is needed to avoid misdiagnoses.

Keywords: thyroid – neovascularization – angiogenesis – vascular proliferation – histologic alternations – fine needle aspiration biopsy – hemangioma – angiosarcoma

Introduction

Fine needle aspiration biopsy (FNAB) of the thyroid gland is a well-established, safe and rapid method for the management of thyroid nodules [1, 2]. Thyroid FNAB is useful to select the patients who need surgical treatment [3, 4]. Clinical complications of FNAB include hematoma formation and acute airway obstruction, which are fortunately uncommon [5, 6].

Previous studies characterise FNAB needle tract related histopathological changes in various organs, including lymph nodes, salivary glands, parathyroid glands and breast [7, 8, 9, 10]. The most common change is infarction or necrosis [11, 12, 13].

Dissemination of malignant cells during FNAB is rare as reviewed by Polyzos and Anastasilakis [14].

LiVolsi and Merino described worrisome histologic alternations following thyroid FNAB (WHAFFT) in 1994 [15]. Several following studies confirmed their observations [16, 17, 18, 19]. Thyroid FNAB related histopathological changes often include haemorrhage, fibrosis, granulation tissue, and necrosis [15, 16, 17, 18, 20, 21]. Necrosis and infarction of the thyroid gland had been already described before the WHAFFT concept mainly as case reports and case series [22, 23].

Vascular changes as a consequence of FNAB have been described sparsely [15, 16, 17, 24, 25]. They include hemangioma-like vascular proliferation, angiosarcoma-like proliferation, papillary endothelial hyperplasia and thrombosis with recanalization [17, 16, 20]. Notably, thyroid vascular tumours as hemangioma and angiosarcoma are remarkably rare [26].

The present study aimed at describing the frequency and histopathological characteristics of vascular proliferation in the thyroid gland histopathological

specimens and its possible relation to the previous FNAB. We present a detailed analysis of 64 cases from a 4-year-period.

Materials and Methods

The study was conducted at the Department of Pathology, Fimlab Laboratories, Tampere University Hospital and was approved by the local Ethical Committee. We reviewed all total thyroidectomy and thyroid lobectomy samples obtained between January 2010 and December 2013 (n=787) for vascular proliferation. The surgical specimens were routinely fixed in 10% formalin and processed into paraffin blocks. The tumour cases were totally blocked. In goitre cases all nodules were sampled, there was a minimum of 3 blocks per lobe. Four- μ m-sections were stained with haematoxylin-eosin. We performed additional immunostainings with primary antibodies detecting the endothelium (CD31, dilution 1:400, clone JC70A, DAKO Denmark, Glostrup, Denmark), lymphatic endothelium (podoplanin, dilution 1:200, clone D2-40, DAKO Denmark, Glostrup, Denmark) and proliferation (Ki-67, clone MIB-1, dilution 1:200, DAKO Denmark, Glostrup, Denmark). We used a fully automated immunostaining system (Bondmax, Leica Biosystems Newcastle Ltd., Newcastle upon Tyne, United Kingdom).

Neovascularization was further analysed for the localization within the thyroid gland, the total area and the dimension of the vessels as well as endothelial characteristics. Also, we evaluated the presence of haemorrhage, thrombosis, fibrin deposits, oedema, fibrosis, necrosis, granulation tissue and cystic degeneration in the tissue around the neovessels.

We used IBM SPSS (version 21.0) for statistical analysis. Significant associations were defined using the chi-square test.

Results

Out of 787 thyroid specimens, vascular proliferation was found in 64 cases (8.1%).

The study population consisted of 43 females and 21 males aged 21-88 years (mean 62 years). The histopathological diagnoses were papillary carcinoma in 6 cases, follicular carcinoma in 7 cases, follicular adenoma in 25 cases, and nodular goitre in 26 cases. In addition to above listed main diagnoses, Hashimoto thyroiditis was diagnosed in 16 cases. Oncocytic metaplasia was found in 28 cases, out of which oncocytic tumour variants were oncocytic papillary carcinoma in 3 cases, oncocytic follicular carcinoma in 4 cases and oncocytic follicular adenoma in 15 cases.

Data on preceding FNAB date and diagnosis was available in 49 cases (76.6%). The frequency of FNAB availability and the distribution of the main diagnoses are comparable between studied cases and the rest of the department specimens.

Radiologists performed ultrasound-guided FNABs with 22-gauge needles. In 40.8% of the cases, FNAB was taken less than two months before the surgery, in total, the FNAB time frame ranged from one month to two years. The dilatation of neovessels correlated with FNAB time span, but no statistical difference was found for total vessel area. In nine cases, FNAB was repeatedly taken twice and in one case three times. The data was unavailable in 15 cases (23.4%), because information was not available for FNABs obtained in private clinics or other regions.

The observed vessels were capillaries, venules and arterioles. The shape of vessels was irregular and dilated. Vessels were mainly clustered (Fig 1a-f). The endothelium was positive for pan-endothelial marker CD31 (Fig 1g-j), but negative with lymphatic endothelium marker podoplanin (Fig 1k) [27]. We did not find mitoses or nuclear atypia in the endothelium. No proliferation activity was seen as detected with Ki-67 in the endothelium and the tissue surrounding vascular structures (Fig 1l).

The newly formed vessels were characterized by dilatation, branching and sprouting with local endothelial irregularities. The areas of neovessels varied among the cases. Only in one case, the area reached 80% of the thyroid gland tissue sections. In 51 cases (79.7%), the neovascularization occupied less than 5% thyroid gland area. In all cases without the FNAB data, the area was <5% and accompanying changes were limited. Of note is that, in 34.7% with FNAB data available, the neovascularized area was $\geq 5\%$ ($p=0.008$). According to the main diagnoses, in 21 nodular goitres out of 24, the area was less than 5%.

We assessed the vessel dilatation into three grades. We found high-grade vessel dilatation in 16 cases (25.0%), moderate grade in 28 cases (43.8%) and low grade in 20 cases (31.3%). The accompanying inflammatory infiltrates of Hashimoto thyroiditis did not influence the vessels characteristics, dilatation, or total area. In fact, the neovessels were not localized in the inflammatory areas.

We found vascular changes within the tumour in 92.0% of adenomas and 61.5% of carcinomas ($p<0.001$). Surrounding tissue harboured vascular changes less often, but still with remarkable frequency. Similarly, in nodular goitres, we found neovasculature within the nodules.

In the majority of those cases, where we observed haemorrhage (90.6%), oedema (84.4%), fibrin deposits (79.7%) and cystic degeneration (65.6%), the FNABs were taken in less than two months before the surgery. Figure 2 shows clustering of the changes (Fig 2).

Surprisingly, we found thrombosis only in 4 cases (6.3%) (Fig 1f) and necrosis in 3 cases (4.7%). Necrotic lesions did not correspond to areas with oncocytic metaplasia. We observed fibrosis in 32.8% of the cases.

Discussion

The thyroid gland is a highly vascularized organ [28]. Vascular endothelial growth factor (VEGF) levels are also high in the thyroid tissue [29]. The diagnostics of thyroid vascular lesions is not straightforward. The heterogeneous disease spectrum consists of reactive lesions like benign endothelial proliferation, benign hemangiomas and extremely rare malignant angiosarcomas [26]. Table 1 represents a literature review of thyroid hemangiomas (Table 1). Outside the endemic alpine area, angiosarcomas and malignant haemangioendotheliomas are uncommon [44, 45]. Table 2 summarises various nontumorous vascular lesions, which are not related to FNAB (Table 2) [46, 47, 48, 49].

Several studies have described the relation of FNAB and vascular proliferation [15, 16, 17, 24, 25, 18] (Table 3). In WHAFFT concept article, however, only dilated vessels were mentioned [15]. Erzos et al. found vascular proliferation and thrombosis in 45% of thyroids that were aspirated, but they did not find these changes in non-aspirated cases [16]. On the contrary, Bolat reported vascular changes only in 2.7% of studied thyroids [18]. In another series, 10 thyroids out of 102 showed vascular changes lead by the thrombosis and recanalization in 5 cases [17]. Of note is that, all the cases of vascular changes were associated with necrosis in contrast to our data. Our own necrosis reported cases were not accompanied by neovascularization [21]. Interestingly, Pandit showed also angiosarcoma-like alterations in a specimen 147 days after FNAB [17]. Erzos et al. [16] did not report nuclear pleomorphism and mitotic figures, which is in agreement with our results. In some cases, plump endothelial cells and endothelial hyperplasia mimic vascular tumours [26, 7]. Due to high vascularity, the thyroid gland is susceptible to a haematoma [24, 16]. The proposed mechanism of the neovascularization is a needle-induced haemorrhage

followed by a haematoma and thrombosis that resolves by re-canalization and vessel formation (Figure 3). Additionally, Pandit suggested that also fibroblastic proliferation, not only vascular, is caused by needle trauma [17]. Traumatization by palpation and surgery is a less probable explanation [24]. Sapino et al. described spontaneous haemorrhage in long-standing goitre nodules [48]. This observation is in agreement with our results, as FNAB history was negative/unavailable in 15 cases in our series. Sharma and Krishnanand speculated about the role of FNAB technique in the aetiology of vascular proliferation: they found a 21-gauge needle less traumatic than other options [19]. The numerous and multiple needle passes increase vascular proliferation development and capsular pseudo-invasion [15, 20] that interferes with follicular adenoma versus carcinoma diagnostics. In our personal experience, the neovascularization did not interfere with the measurements of nodule/tumor size. In the literature, needle tract effect after repeated thyroid FNAB was also described in cytological specimens. In a study by Recavarren et al., 16 cases of Bethesda atypia of undetermined significance (AUS/FLUS) in repeated FNAB was found [51]. They found two samples with atypical stromal, endothelial and follicular cells embedded in blood or blood clots, probably induced by previous FNABs. In our opinion, revision of previous slides is necessary to avoid inaccuracies in diagnostics. The cases may nevertheless be categorised into the AUS/FLUS heterogeneous group [52].

Core needle biopsy (CNB) provides an alternative diagnostic method in nondiagnostic and AUS/FLUS cases [53]. However, thyroid CNB is not widely used in clinical practise. The commonest clinical complication is haematoma formation [54, 55]. We suspect that the CNB procedure can cause similar and even worse histopathological alterations than the FNAB procedure.

In conclusions, post FNAB changes are often accompanied by dilated newly formed vessels. Proper histopathological diagnostics requires the knowledge of reactive post-FNAB tissue alterations and patient history of FNAB to avoid misdiagnosis. Pathologists should differentiate reactive vascular changes from rare thyroid vascular tumours. In the clinical practice, the differential diagnosis with angiosarcoma is of paramount importance. However, a secondary hemangioma caused by the organisation of a hematoma is almost impossible to distinguish from a real hemangioma [26]. Nevertheless, the phenomenon of neovessels is quite rare in thyroid gland specimens.

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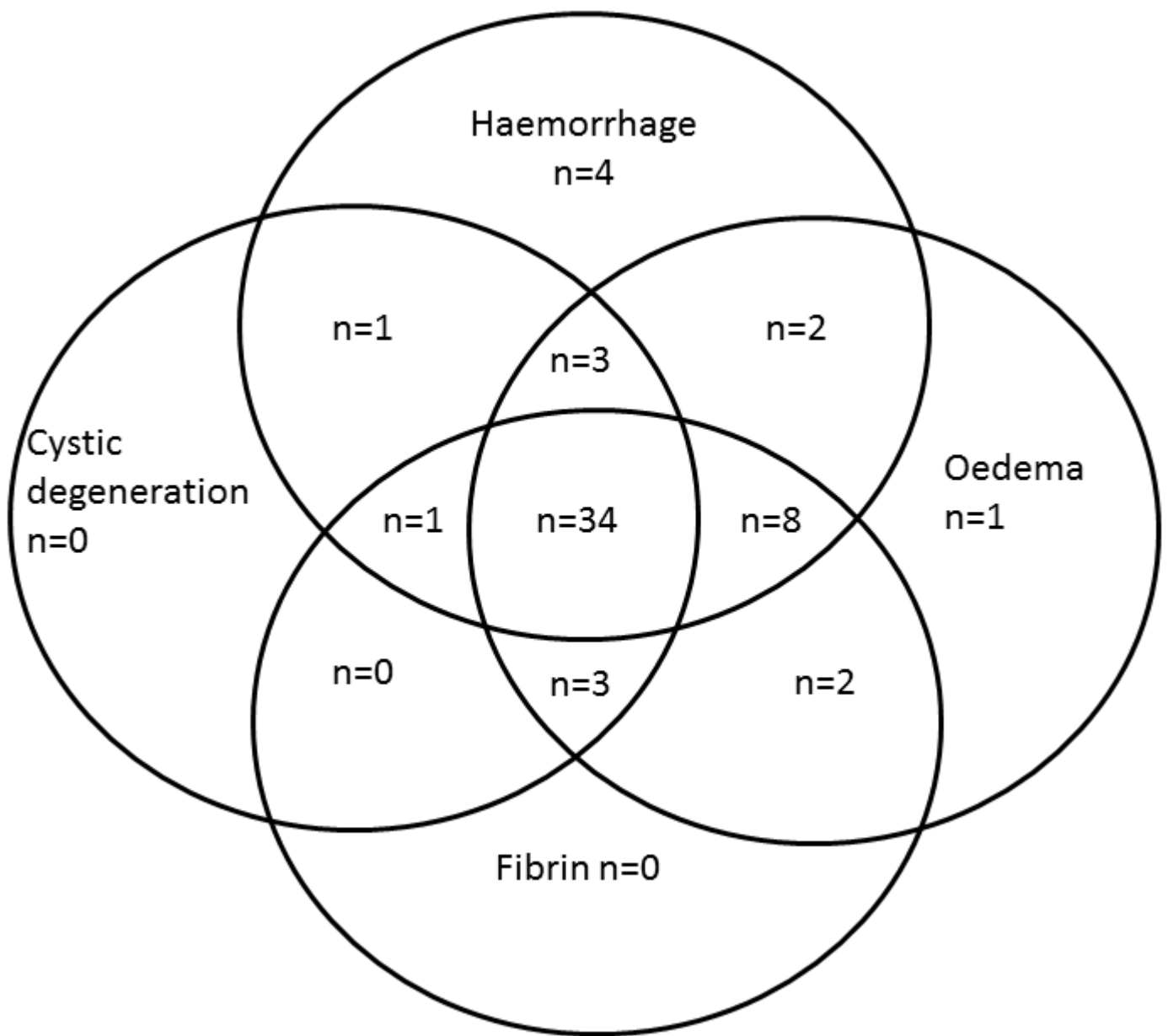


Figure 1 Co-presence of haemorrhage, oedema, fibrin deposits and cystic degeneration with vascular proliferation in presented study.

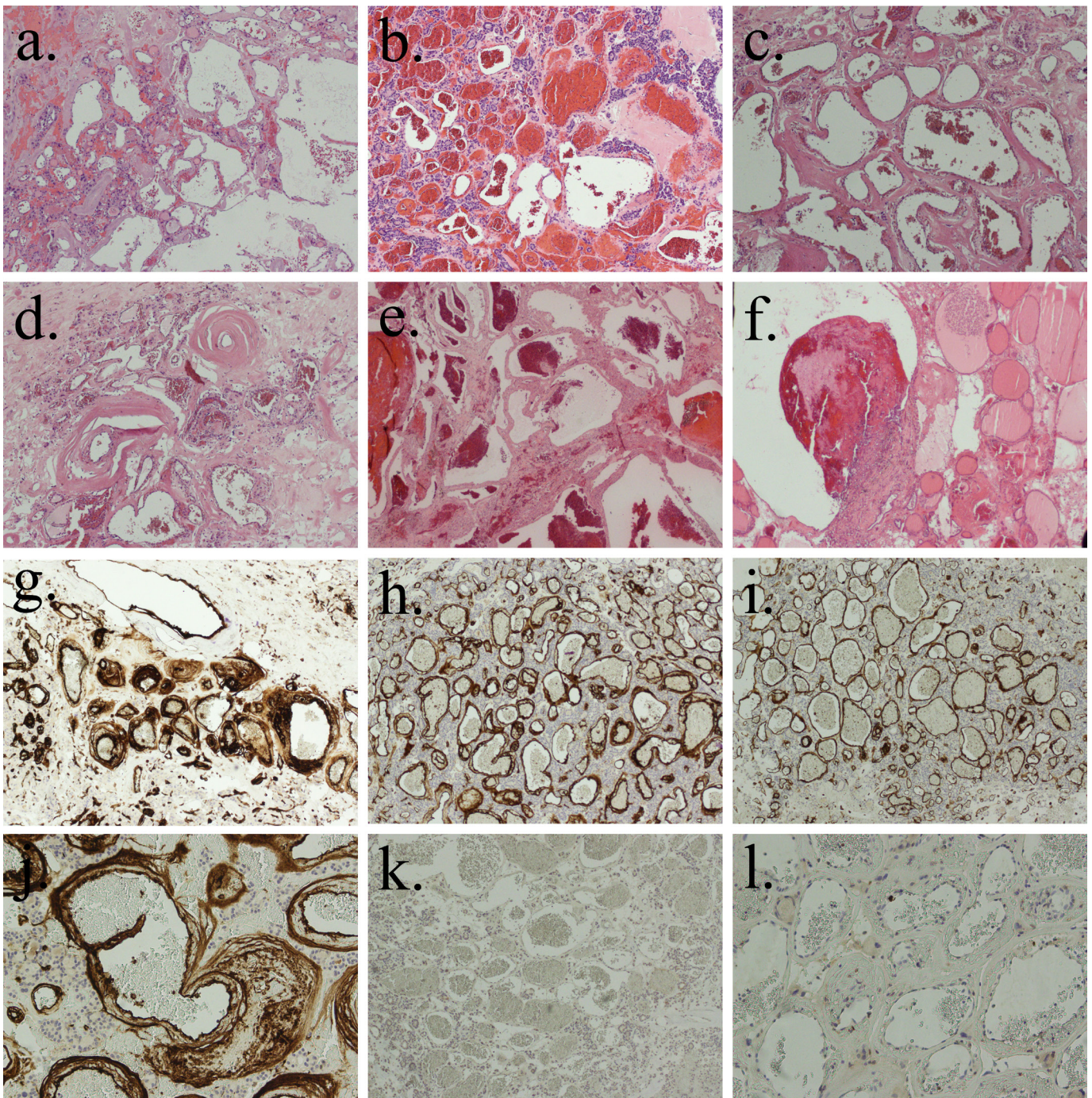


Figure 2 Histopathological and immunohistochemical characteristics of vascular proliferation: a. Dilated thin-walled capillaries surrounded by haemorrhage and cystic degeneration in nodular goitre (haematoxylin-eosin, magnification 40×), b. Dilated mainly blood-filled capillaries in a fibrin-rich hemorrhagic area in nodular goitre (haematoxylin-eosin, magnification 40×), c. Dilated vessels with fibrin-rich walls represent arteriole/venule levels. The case of follicular adenoma. (haematoxylin-eosin, magnification 20×), d. Area of oedema, haemorrhage and onion-like fibrin deposits surrounding dilated capillaries in follicular adenoma (haematoxylin-eosin, magnification 20×), e. Clusters of dilated capillaries in a hemorrhagic area in an oncocytic variant of follicular adenoma (haematoxylin-eosin, magnification 40×), f. A thrombotic vessel in the vicinity of papillary carcinoma (haematoxylin-eosin, magnification 100×), g. Thick-walled fibrin-rich CD31-positive vessels in follicular carcinoma (CD31 immunohistochemistry, 40×), h. Numerous irregular venules or arterioles revealed CD31-positivity in nodular goitre (CD31 immunohistochemistry, 40×), i. Dilated irregular capillaries showed features of branching in another goitre case (CD31 immunohistochemistry, 100×), j. Irregular thickened walls of newly formed vessels in goitre case (CD31 immunohistochemistry, 200×), k. No lymphatic vessels were found in vessel-rich areas (podoplanin- immunohistochemistry, 100×), l. Proliferation activity as detected with Ki-67 antibody was sparse in newly formed vessels (Ki-67 immunohistochemistry, 100×).

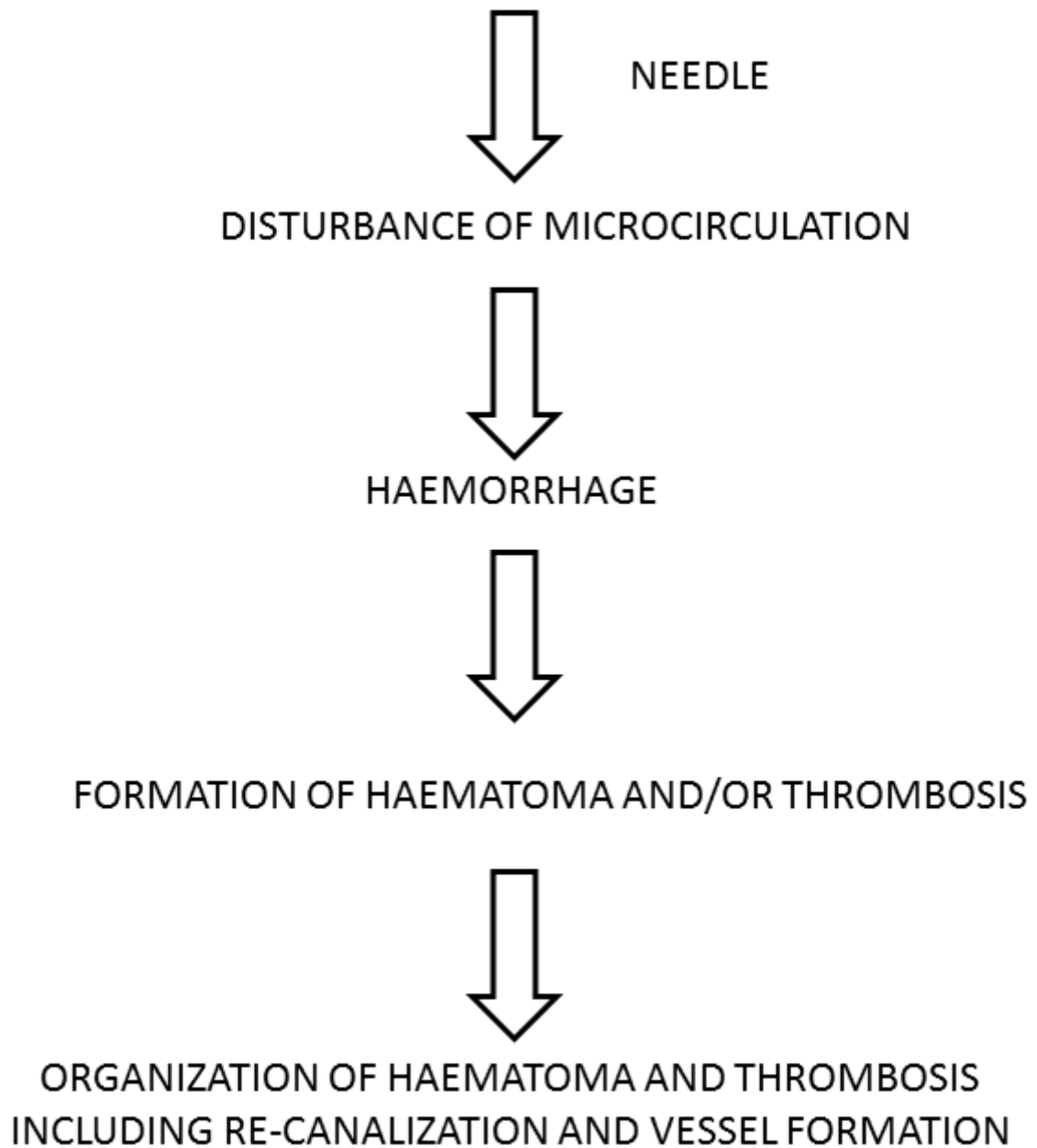


Figure 3 Mechanism of Vascular Proliferation Development

Table 1 Thyroid gland hemangiomas

Citation	Pathological Diagnosis	Size (cm)	Sex	Age	FNA history	Histologically verified
Pickleman et al. [30]	primary hemangioma/hemangioma NOS	7,5X3X2	M	56	no	yes
Pendse et al. [31]	primary hemangioma	6X3,5	M	53	yes	yes
Kumar et al. [32]	primary hemangioma	4X4	M	53	no	yes
Rios et al. [33]	cavernous hemangioma	5X4	F	48	no	yes
Rios et al. [33]	cavernous hemangioma	5X3	F	63	no	yes
Kano et al. [34]	cavernous hemangioma	5,5X3,0X2,0	M	21	no	yes
Hassan et al. [35]	epithelioid hemangioendothelioma	5,0X8,0X4,0	F	73	-	yes
Lee et al. [36]	cavernous hemangioma	17,0X16,5	M	66	no	yes
Datta et al. [37]	cavernous hemangioma	4,9X4,4	M	25	no	yes
Ciralik et al. [38]	cavernous hemangioma	7X6X6	M	64	no	yes
Sakai et al. [39]	cavernous hemangioma	5,2X4,8X3,5	F	71	no	yes
Michalopoulos et al. [40]	cavernous hemangioma	3,7	M	78	no	yes
Gutzeit et al. [41]	cavernous hemangioma	4	F	84	no	yes
Maciel et al. [42]	cavernous hemangioma	22X21X17	F	80	no	yes
Dasgupta et al. [43]	cavernous hemangioma	4,5X4	M	38	no	yes

Table 2: Nontumorous vascular changes not related to FNA

Citation	Pathological Diagnosis of vascular lesion	Number of cases	Co-existing thyroid pathology	FNA history
Tse et al. [46]	Capsular intravascular endothelial hyperplasia	3	Follicular carcinoma (n=2) Papillary carcinoma (n=1)	1 (33%)
Schmitz et al. [47]	Florid capsular and pericapsular papillary endothelial proliferation	1	Poorly differentiated carcinoma	1 (100%)
Sapino et al. [48]	Intranodular reactive endothelial hyperplasia	11	Adenomatous goitre	1 (9%)
Baloch and LiVolsi [49]	Intravascular Kaposi's-like spindle cell proliferation	3	Follicular carcinoma (n=3) including oncocytic variant (n=2)	1 (33%)

Table 3 Vascular Proliferation after Thyroid FNAB: Review of Literature

Source	All cases (n)	Vascular changes cases in total (n)	Vascular proliferation (n)	Vascular thrombosis (n)	Papillary endothelial hyperplasia	Plump endothelial cells
Ersöz et al. [16]	20	9 (45%)	9 (45%)*	9 (45%)*	N.D.	N.D.
Pandit and Phulpagar [17]	265	10 (3.8%)	2 (0.7%)	5 (4.9%)	3 (2.9%)	N.D.
Tsang and Duggan [24]	2	2 (100%)	2 (100%)	2 (100%)	2 (100%)	2 (100%)
Sharma and Krishnanand [19]	100	23 (23%)	4 (4%)	20 (20%)	4 (4%)	1 (1%)
Bolat et al. [18]	150	14 (9%)	4 (2.7%)	10 (6.7%)	N.D.	N.D.
Ramraje and Kambale [50]	2	2 (100%)	1 (50%)	0	1 (50%)	1 (50%)
Baloch and LiVolsi [25]	250	N.D.	N.D.	N.D.	N.D.	N.D.
LiVolsi and Merino [15]	300	N.D.	N.D.	N.D.	N.D.	N.D.

*reported as vascular proliferation and/or vascular thrombosis